Adult-onset dystonia with marfanoid features

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A 43-year-old Asian American man with asthma and hypertension was referred to the movement disorder center with a 5-year history of gradually progressive action-induced ankle inversion followed by trunk tightness and painful neck twisting with right shoulder elevation. He was born in the United States and successfully graduated college as a B/C student with mild learning difficulties. He always had disproportionately long limbs and digits and at age 12 developed ectopia lentis (medial-inferior displacement). Numerous ocular surgeries were performed including intraocular lens exchange with iris fixation. Marfan syndrome was previously diagnosed based on physical findings. There was no family history of Marfan syndrome, marfanoid features, or early death due to aortic dissection. *FBNI* mutations were not tested and serial echocardiograms demonstrated no aortic root dilation. Diagnosis was later refined to ectopia lentis syndrome per updated guidelines. At age 29, he required allograft repair of an anterior cruciate ligament following minor impact. Four years later, while walking, he had musculoskeletal trauma in the left foot with subsequent toe extension weakness. Nerve conduction studies confirmed absence of compound motor action potentials in the left peroneal nerve lateral terminal branch. At age 38, he developed left foot pain with tendency for dorsiflexion and ankle inversion when walking. Severity gradually progressed and tightness extended to the trunk within 2 years. At age 41, he developed elevation of the right shoulder and several weeks later rightward rotation of the neck and back. Dystonia gradually progressed. Symptoms were exacerbated by stress but not relieved by alcohol or muscle relaxers.

Pertinent physical examination findings include normal attention and memory, reduced visual acuity, pectus carinatum, marfanoid habitus with arachnodactyly, and 0/5 left foot toe extensor strength with generalized dystonia (video at Neurology.org/cp). Dystonia affected the left lower extremity (ankle dorsiflexion and inversion), trunk (lateral-anterior tilt), and neck (laterocollis and retrocollis with intermittent irregular tremor). There was subtle symmetrically increased signal in the pallidum on brain MRI susceptibility-weighted sequences, considered as normal variability. Initial laboratory results demonstrated elevated total plasma homocysteine (151 $\mu\text{mol/L}$, reference 5–15), urine homocysteine (380.6 $\mu\text{mol/g}$ creatinine, reference 0–2), and serum methionine (745 $\mu\text{mol/L}$, reference 10–50). Sequencing of the cystathionine β -synthase (CBS) gene revealed a novel homozygous frameshift mutation in exon 5 designated as c.402delG, which predicts a premature stop codon 2 amino acids downstream from the mutation site (p.T135Rfs*2). Based on American College of Medical Genetics and Genomics standards, the frameshift variant and predicted protein truncation are very strong evidence for mutation pathogenicity (*PVS1*).

Practical Implications

Consider homocystinuria in the differential diagnosis of adult-onset dystonia and preexisting ectopia lentis or marfanoid habitus.

Video

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Figure Homocysteine catabolism affected by cystathionine β -synthase deficiency

B₆ = vitamin B₆ (pyridoxine); B₁₂ = vitamin B₁₂ (cobalamin); BHMT = betaine-homocysteine S-methyltransferase; DMG = dimethylglycine; MS = methionine synthase; MTHF = methyltetrahydrofolate; SAH = S-adenosylhomocysteine; SAM = S-adenosylmethionine; THF = tetrahydrofolate.

DISCUSSION

Homocystinuria due to CBS deficiency results from an inborn error of the transsulfuration pathway characterized by increased plasma homocysteine and methionine with decreased cysteine. It commonly presents in childhood with developmental delay, intellectual disability, ectopia lentis, severe myopia, and marfanoid skeletal features and is now increasingly diagnosed through newborn screening. Up to 27% have thromboembolism before age 15, especially if suboptimally treated.¹ In this case, combination of learning disability, ectopia lentis, marfanoid features, and paradoxical musculoskeletal injuries should have prompted early consideration of homocystinuria. Dystonia uncommonly occurs in homocystinuria and may reflect thromboembolic disease, but reports of children do not always demonstrate brain imaging abnormalities.² One report of an adult patient with homocystinuria documented relapsing-remitting dystonia corresponding to biochemical marker levels, implying metabolic etiology.³ In our case, a novel gene mutation was observed in the *CBS* gene, which encodes an enzyme that conjugates homocysteine and serine to form cystathionine, the first irreversible step of homocysteine catabolism (figure).

Early detection of homocystinuria is critical since both pyridoxine responders and nonresponders exhibit reduced morbidity and mortality. Our case is a novel late onset of secondary dystonia in homocystinuria without intracranial thromboembolic events and suggests homocystinuria should be included in the differential diagnosis of patients with classic phenotypic

traits who present with neurologic manifestations such as secondary dystonia, seizure, or psychiatric/cognitive disorders.⁴ Late-onset dystonia may represent variability in gene expression, intrinsic properties of the novel genetic mutation, or variability in natural history. Others suggest dystonia results directly from accumulation of sulfur-containing compounds in basal ganglia,⁵ or indirectly through disturbances of neurotransmitter balance.²

Our patient's total plasma homocysteine reduced 23% after pyroxidine challenge and he currently receives betaine, B₁₂, folate, pyridoxine, and botulinum toxin injections to reduce risk of atlantoaxial subluxation given retrocollis with known connective tissue abnormalities.⁶ Additional therapeutic efforts are ongoing to aggressively reduce thromboembolic risk factors. Deep brain stimulation might be considered should botulinum toxin not provide effective benefit for progressive dystonia.⁷

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AUTHOR CONTRIBUTIONS

Scott A. Norris: drafting and revising the manuscript for content. Anja Pogarcic: acquiring and editing video data, revising the manuscript for content. Matt Hicks: editing video and revising manuscript for content. Joel S. Perlmutter: revising the manuscript for content. Marwan Shinawi: drafting and revising the manuscript for content.

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